UNITED STATES ENVIRONMENTAL PROTECTION AGENCY,
WASHINGTON, D.C. 20460

004567

NOV 7

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

To: E. Budd, Group Leader TS-769

From: Bernice Fisher, Statistician and
B. Litt, Team Leader, Biostatistic Team

Thru: R. Engler, Chief, Mission Support Staff

Subject: Statistical Evaluation of Summary Rat Oncogenicity Data for Fenpropathrin

The number of tumor-bearing rats tabulated by sex and dose group for a two-year period for about two dozen individual tissues (e.g. mammary gland, liver, etc.) are presented in company tables 5 through 12 (see attached tabulations). No detailed data are presented on specific tumor types (i.e. carcinomas, adenomas, etc.). For commonly expected tumors (i.e. 2-5 percent) in these tissues, there is no evidence of oncogenicity associated with doses of fenopropathrin over the two years.

Statistical evaluations (i.e. Fisher's Exact Test at $p \leq .05$) of treatment groups (1, 5, 125 and 500 ppm) for each individual tissue, both sexes, with controls yielded no evidence of significant differences.

Since the number of tumor-bearing animals was sparse in the 500 ppm dose group, the 125 ppm treatment group was added to it. Again, comparison of controls with the treatment group (125 ppm plus 500 ppm) demonstrated no statistically significant differences at the $p \leq .05$ level in any of these tissues, either for males or females.

In reviewing the tabular data in summary, both for the total number of neoplasias and the malignant tumors alone, statistical evaluation (Fisher's Exact Test at $p \leq .05$), once again indicated no significant differences.

In conclusion, as there are only 25 animals per sex and dose group, these data do not provide the guideline required level of assurance that no effect may be expected at 500 ppm. However, when the 500 and 125 ppm groups are combined the resulting group of 50 animals provides this assurance at the 125 ppm dose level.

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MEMORANDUM

SUBJECT: EPA Registration No. 39398-RA: Fenpropathrin (Danitol™) insecticide/miticide. Request to register a new synthetic pyrethroid-like derivative for formulating use only.

Tox Chem No. 273H

TO: T. A. Gardner
Product Manager #17
Registration Division (TS-767)

FROM: John Doherty 4/2/85
Toxicology Branch
Hazard Evaluation Division (TS-769)

THRU: E. R. Budd, Section Head
Toxicology Branch
Hazard Evaluation Division (TS-769). Budd 7/17/85 7/22/85

Background:

Sumitomo Chemical America, Inc. is requesting to register their product, DANITOL™ TECHNICAL, an insecticide and miticide, for formulating use only. A battery of studies were submitted to support this registration and were reviewed (see below). Fenpropathrin is a new pesticide chemical of the synthetic pyrethroid-like derivative class.

Recommendations and Comments:

1. Before TB can recommend in favor of registration of DANITOL® Technical for formulating use only, certain problems related to labeling and potential inhalation hazard must be resolved.

The available acute inhalation LC_{50} data were obtained from an unspecified formulation, but the data indicated that fenpropathrin is very toxic by the inhalation route (LC_{50} = 0.043 mg/l for female mice). Although no LC_{50} was determined for rats, there were signs and symptoms of poisoning at the highest dose level tested (0.096 mg/l). Because Tox Cat I is 0.2 mg/l or less, the current signal word and precautionary labeling for this product is considered inappropriate.

The label signal word must be changed to Tox Cat I and the signal word DANGER together with the skull and crossbones added to the label. The precautionary labelling must be changed to include the appropriate statements for a product that may be a Toxicity Category I inhalation hazard.

The registrant is welcome to justify the current label signal word in terms of acute inhalation toxicity and hazard. In particular, the registrant must explain in detail that the technical material does not result in respirable vapors or represent any hazard to workers preparing formulations from it. Alternatively, the registrant may provide another LC_{50} study which demonstrates that the technical material belongs in some other toxicity catogory based on inhalation toxicity.

The following comments (below) will have to be addressed by the registrant and/or additional data or information submitted for the studies indicated prior to the registration of the various formulated products containing fenpropathrin, depending upon the end-use or if tolerances for fenpropathrin are requested. Other comments below are listed to discuss some of the aspects of the nature of the toxicity of fenpropathrin. These comments relate only to the studies thus far reviewed by TB. Additional studies may be required depending upon the registrations sought.

2. Rat chronic feeding/oncogenicity study. CORE classification of the chronic feeding aspects of this study is RESERVED. CORE classification of the oncogenicity aspects of this study is CORE MINIMUM.

   The NOEL (for chronic feeding aspects) is tentatively set at 1 part per million. At 5 ppm and above there are noted higher incidences of a lesion in the lungs of males described as "medial muscle hypertrophy." The nature of this lesion must be further clarified. The registrant should be asked to present a more detailed description of this lesion type together with historical control data and a defense that this lesion is not related to ingestion of fenpropathrin.

   No obvious oncogenic effect of fenpropathrin was evident in this study.

3. The rabbit teratology study was classified as CORE SUPPLEMENTARY. A new study at higher dose levels will be needed to meet the requirement for a teratology study in rabbits when registrations are sought which require two teratology studies.

4. Neurotoxicity in rats. A subacute feeding study in rats indicated that nerve fiber lesions developed when the rats were dosed with 900 ppm after only a few days of feeding. Certain other pyrethroid insecticides are also known to cause this effect The study showing these lesions tested only a single dose level and no NOEL for these lesions was demonstrated. Additional subchronic and chronic feeding studies were conducted at lower dose levels. No signs of nerve fiber degeneration were reported in these subsequent studies in which special staining techniques for nerve fiber lesions were used.

   TB recognizes that fatal or near fatal dose levels of fenpropathrin may produce nerve fiber lesions. Since other studies demonstrate NOEL's for nerve lesions (i.e., the chronic feeding study indicated a NOEL of 500 ppm), no additional investigations are required to further define the potential of fenpropathrin to produce nerve lesions in rats.

5. The dog subchronic feeding study did not show a clear NOEL. At the lowest dose level tested (250 ppm), there were more incidences of emesis in both males and females when compared to the control groups. Similar responses of increased incidences of emesis have been known to be associated with other pyrethroids and this effect was considered in setting the NOEL for ~~the~~ these other chemicals. In the absence of a suitable demonstration that fenpropathrin is not affecting the vomiting center of the dog, this effect is considered a toxic response.

   The subchronic dog feeding study need not be repeated. The dog chronic feeding study (one year or longer) should be designed to assess the NOEL for this effect and should include a dose level below the 250 ppm level used in this study.

6. Mutagenicity Studies. Some of the mutagenicity studies submitted were found to be either inconclusive or unacceptable based on current review criteria and discussion with Dr. I. Mauer, Geneticist, TB. The following mutagenicity study types are recommended in addition to the studies already submitted.

   i. bacterial mutagenicity test (Ames test) without metabolic activation.

   ii. an in vitro chromosome aberration test.

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Front Panel

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DANITOL (TM) TECHNICAL

INSECTICIDE & MITICIDE FOR FORMULATION USE ONLY

ACTIVE INGREDIENT:

Fenpropathrin (α cyano-3-phenoxybenzyl 2,2,3,3-tetramethyl cyclopropanecarboxylate)	90.0%
INERT INGREDIENTS	10.0%

WARNING

SEE SIDE PANEL FOR PRECAUTIONARY STATEMENTS

STATEMENT OF PRACTICAL TREATMENT

IF SWALLOWED, call a physician or Poison Control Center. Drink 1 or 2 glasses of water and induce vomiting by touching back of throat with finger. Do not induce vomiting or give anything by mouth to an unconscious person.

IF ON SKIN, wash with plenty of soap and water. Get medical attention if irritation persists.

IF IN EYES, flush with plenty of water. Get medical attention if irritation persists.

Net Contents _____

EPA Registration No. 39398-

EPA Est. No. 10308-JP-2

Made for: Sumitomo Chemical America, Inc.
345 Park Avenue
New York, New York 10154

Registered Trademark of Sumitomo Chemical America, Inc.

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PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS AND DOMESTIC ANIMALS

WARNING

May be fatal if swallowed or absorbed through skin. Causes moderate but temporary eye injury. Do not get in eyes, on skin or on clothing. Wear protective clothing and rubber gloves. Wash throughly with soap and water after handling and before eating or smoking. Remove contaminated clothing and wash before reuse.

ENVIRONMENTAL HAZARDS

This product is extremely toxic to fish and aquatic organisms. Do not discharge into lake, streams, ponds or public waters unless in accordance with an NPDES Permit. For guidance, contact your Regional Office of the Environmental Protection Agency.

STORAGE AND DISPOSAL

1. STORAGE: In cool, dry area, keep containers closed when not in use. In case of spills or leaks, soak up with sand, earth or synthetic absorbent and dispose of in compliance with Federal, State or local procedures.

2. PROHIBITIONS: Do not contaminate water, food or feed by storage or disposal.

3. PESTICIDE DISPOSAL: Pesticide, spray mixture or rinse water that cannot be used according to label instructions must be disposed of according to applicable Federal, state or local procedures.

4. CONTAINER: Triple rinse (or equivalent). Then offer for recycling or reconditioning, or puncture and dispose of in a sanitary landfill, or by other approved state and local procedures.

[redacted]

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labelling.

Refer to technical literature for formulation of Danitol(TM) Technical for end uses.

Formulators who use this product may be responsible for providing data to support their own registration with the appropriate regulatory agencies.

NOTICE - READ CAREFULLY

CONDITIONS OF SALE:

Sumitomo (and seller) offer(s) this product for sale subject to, and buyer and all users are deemed to have accepted, the following conditions of sale and warranty which may only be varied by written agreement of a duly authorized representative of Sumitomo.

WARRANTY LIMITATION:

Sumitomo warrants that this product conforms to the chemical description in the directions for use on the label subject to the inherent risks referred to below. Sumitomo makes no other express warranties: THERE IS NO IMPLIED WARRANTY OF MERCHANTABILITY and there are no warranties which extend beyond the description on the label hereof.

INHERENT RISKS:

The directions for use of this product are believed to be reliable and should be followed carefully. However, it is impossible to eliminate all risks associated with use. Buyer assumes all risks associated with use or application of this product contrary to label instructions or resulting from extraordinary weather conditions.

LIMITATION OF LIABILITY:

In no case shall Sumitomo be liable for special, indirect or consequential damages resulting from the use or handling of this product and no claim of any kind shall be greater in amount than the purchase price of the product in respect of which such damages are claimed.

Studies Reviewed

Study	Result	Core Classification
Acute oral LD_{50} - rats	70.6 mg/kg males 66.7 mg/kg females (in corn oil). (91.8% ai) (Tox Cat II)	Guidelines
Acute oral LD_{50} - rats	54.0 mg/kg males 48.5 mg/kg females (in corn oil) (97.0% ai) (Tox Cat I)	Minimum
Acute oral LD_{50} - rats	164 mg/kg males 107 mg/kg females (in gum arabic) (97.3% ai) (Tox Cat II)	Guidelines
Acute oral LD_{50} - mice	67 mg/kg males 58 mg/kg females (in corn oil)	Minimum
Acute oral LD_{50} - rabbits	675 mg/kg males 510 mg/kg females (in corn oil)	Minimum
Acute oral LD_{50} - dogs	> 1000 mg/kg	Supplementary
Acute intravenous LD_{50} - mice	4.5 (3.9-5.3) mg/kg	Invalid
Acute subcutaneous LD_{50} - rats	1,410 mg/kg males 900 mg/kg females	Minimum
Acute subcutaneous LD_{50} - mice	1,350 mg/kg males 900 mg/kg females	Minimum
Acute intraperitoneal LD_{50} - rats	225 mg/kg males 180 mg/kg females	Minimum
Acute intraperitoneal LD_{50} - mice	230 mg/kg males 210 mg/kg females	Minimum
Acute dermal LD_{50} - rats	1600 mg/kg males 870 mg/kg females	Minimum
Acute dermal LD_{50} - mice	740 mg/kg males 920 mg/kg females	Minimum

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Studies Reviewed

Study	Result	Core Classification
Acute dermal LD_{50} - rabbits	> 2000 mg/kg both sexes (Tox Cat III)	Minimum
Acute inhalation LC_{50} - rats	> 96 mg/m^3 both sexes (Tox Cat I)	Supplementary
Acute inhalation LC_{50} - mice	100 mg/m^3 males 43 mg/m^3 females	Supplementary
Primary ocular irritation - rabbits	No corneal involvement (Tox Cat III)	Guidelines
Primary dermal irritation - rabbits	P.I.S. = 0 (Tox Cat IV)	Guidelines
Skin sensitization - guinea pigs	Not a sensitizer	Minimum
Skin sensitization - guinea pigs (Buehler method)	Not a sensitizer	Minimum
Neurotoxicity - hens	No delayed type neurotoxicity to hens at doses up to 1.0 gm/kg/day for 5 days.	Minimum
Neurotoxicity - rats	Axonal swelling and disintegration noted at 900 ppm (only level tested). No NOEL established. Numerous mortalities.	Supplementary
3-Month feeding - rats	NOEL = 300 ppm. LEL = 600 ppm. Body weight reduction (females), body tremors, decreased kaolin - cephalin clotting time (females), increase in alkaline phosphatase, K^+ level increase in blood (males); brain (females), and kidney (males) weight increase.	Minimum
3-Month feeding - rats	[NOEL = 250 ppm (HDT).]	Supplementary

Studies Reviewed

Study	Result	Core Classification
3-Month feeding - dogs	NOEL < 250 ppm, at this level there are effects on the G.I. tract (emesis, loose stools). At 500 ppm there is also weight loss (females) and body tremors. Also at 750 ppm increased [redacted] weight loss, ataxia, tremors, salivation, and changes in RBCs.	Minimum
21-Day dermal - rabbits	Only effects noted were mild local irritation at site of application.	Guidelines
14-Day feeding and microsomal induction assay - rats	Fenpropathrin did not induce the microsomal monooxygenase system at dose levels up to and including 1000 ppm.	Acceptable
3-Generation Reproduction - rats	NOEL = 25 ppm, LEL = 250 ppm, changes in pup weight.	Minimum
Teratology - rats	Not teratogenic at, up to, and including 10 mg/kg/day (HDT). Maternal NOEL = 0.4 mg/kg/day.	Minimum
Teratology - rabbits	Not teratogenic at, up to, and including 6.0 mg/kg/day (HDT).	Supplementary
2-Year chronic feeding/ oncogenicity - rats	Tentative NOEL = 1 ppm. Tentative LEL = 5 ppm for "medial muscle hypertrophy" in males. LEL = 500 ppm (body weight changes in females).	Chronic Feedin [Reserved] Additional Information Requested Oncogenicity MINIMUM

Studies Reviewed

Study	Result	Core Classification
Metabolism - rats (2 studies)	Fenpropathrin is rapidly metabolized and excreted, major metabolites in urine, feces, and bile identified.	Minimum
Mutagenesis - DNA Repair in mammalian cells	No evidence of a positive response.	Inconclusive
Mutagenesis - Mammalian cell test in vitro	Equivocal result. Test shows slight positive response.	Acceptable
Mutagenesis - DNA damaging capacity with Bacillus subtilis	No evidence of a positive response.	Acceptable
Mutagenesis - Chromosome studies in Chinese hamster bone marrow cells	No evidence of a positive response.	Inconclusive
Mutagenesis - Salmonella tests (metabolic activation only)	No evidence of a positive response.	Unacceptable
Mutagenesis - host mediated assay	No evidence of a positive response.	Unacceptable
Acute oral LD_{50} - mice (10% EC product)	162 (144-182) mg/kg males 164 (148-182) mg/kg females	Supplemental
Acute oral LD_{50} - mice (impurities - see review for structures)	Both have LD_{50} >5000 mg/kg.	Minimum
Acute oral LD_{50} - mice (2,2,3,3-tetramethyl cyclopropane carboxylic anhydride)	1450 (1280-1630) mg/kg males 1880 (1450-2430) mg/kg females	Minimum

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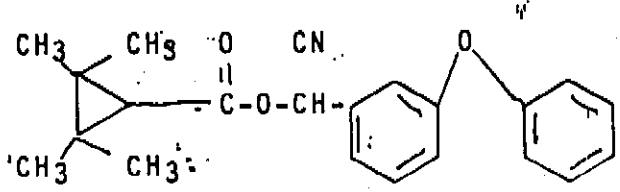
Substance Identification:

1. Chemical name = -cyano-3-phenoxbenzyl 2,2,3,3 tetramethylcyclopropanecarboxylate.

2. Synonyms: fenpropathrin, S-3206, WL-41706.

3. Purity of technical material = 91.8% to 97% depending upon the batch.

4. Structure:



4a. Empirical formula $C_{22}H_{23}NO_3$

4b. Molecular weight 349.4

5. Other physical/chemical data

a. density (at 20°C) = 1.103

specific gravity:

$$d_{20}^{20} = 1.105$$

b. color = yellow to brown liquid or solid.

c. CAS number: 29515-41-8. Shaughnessy number: not provided.

d. vapor pressure: not provided.

e. solubility = 0.34 ppm in water, more soluble in polar organic solvents.

f. chemical class = synethetic pyrethroid-like derivative.

Review of Studies

Acute Oral Toxicity of S-3206 (91.8%) in Rats

Sumitomo Chem. Co., FT-30-0081, Jan 17, 1983
EPA Accession No. 249937; Tab IV-A-1.

9 groups of 10 males and 10 female Sprague-Dawley rats were dosed by gavage with either 0, 10, 25, 50, 60, 72, 86, 104 or 125 mg/kg of test material (S-3206, technical grade, lot no. 2TC019, of 91.8% purity). The rats were fasted 20 hours before dosing and 14 days were allowed for observation. The test material was dissolved in corn oil. The following LD_{50}'s resulted (with 95% confidence limits):

70.6 (53.7 to 92.7) mg/kg for males
66.7 (50.6 to 87.9) mg/kg for females

Signs of intoxication were reported as being evident in rats dosed with 25 mg/kg and above. The signs included muscular fibrillation, soft feces, diarrhea, tremor, decreased spontaneous activity, ataxia, limb paralysis, irregular respiration, salivation (slight) and urinary incontinence. The signs developed an hour or so after dosing but the rats recovered after 3 days. Deaths resulted on the day of dosing or on the day after dosing. Some "slight" depressions in body weight were reported. No "remarkable test compound related macroscropic changes" were reported at gross necropsy.

This study is CORE GUIDELINES. The technical material (as 91.8% pure) is Tox Cat II, however the acute toxicity is close to borderline Tox Category I.

Acute Oral Toxicity of S-3206 in Rats

Sumitomo Chem. C., FT-50-0018, Jan 1979
EPA Accession No. 249937, Tab IV-A-2.

9 groups of 10 male and 8 groups of 10 females were dosed with test material (S-3206, lot # 022018, and 97.0% purity) by gavage at either 15, 20, 30, 50, 59, 77, 100, 120 or 169 (males only) mg/kg and observed for 14 days. The test material was dissolved in corn oil. The LD_{50}'s with 95% confidence intervals were calculated as follows:

54 (43.5 - 67.0) mg/kg for males
48.5 (37.6 - 62.6) mg/kg for females

The toxic signs were listed as being "decrease of spontaneous motor activity, hypersensitivity, fibrillation, tremor, clonic convulsion, salivation, lacrimation, incontinence, hind limb ataxia." The deaths resulted "within 24 hours" and the signs of intoxication disappeared in "24-48" hours. The minimum toxic dose was found to be 20 mg/kg. No chemical related changes were reported at autopsy.

This study is CORE MINIMUM. Most of the data are in summary form. The symptoms and autopsy report are in narrative form. The data provided information sufficient to classify the 97% technical material as Tox Cat I.

Acute Oral Toxicity of S-3206 in Rats

Sumitomo Chem. Co., FT-20-0076, Sept. 24, 1982
EPA Accession No. 249937, Tab IV-A-2.1

8 groups of 10 male and 10 female fasted Sprague-Dawley rats were dosed with test material (S-3206, lot number T-1 and 97.3% purity) by gavage. The test material was dissolved in 10% gum arabic. The dose levels administered were 0, 25, 50, 90, 120, 160, 220 and 300 mg/kg. The rats were observed for 14 days after dosing. The acute oral LD_{50}'s with 95% confidence intervals were determined to be:

164 (115 - 234) mg/kg for males
107 (69.8 - 164) mg/kg for females

Toxic signs were noted at 50 mg/kg and above and included muscular fibrillation, tremor, ataxia, limb paralysis, irregular respiration, lacrimation, salivation, urinary incontinence, diarrhea and other signs. Some signs of decreased weight gain (slight) were noted in the rats receiving 220 mg/kg. No dose related grossly observable lesions were noted.

The study is CORE GUIDELINES. The gum arabic reduces the toxicity of the test material (see previous study above). The test material (97.3% technical) may be classified as Tox Cat II.

Acute Oral LD_{50} Toxicity of S-3206 Technical in Mice

Sumitomo Chem. Co., FT-50-0035, March 21, 1975
EPA Accession No. 279937, Tab IV-A-3

4 groups of 10 male and 10 female 7-8 week old mice were dosed with either 30, 45, 67 or 100 mg/kg of test material (S-3206, lot 022078, purity 97.0%). The test material was dissolved in corn oil and the mice were observed for 14 days. The following LD_{50}'s with 95% confidence intervals were determined.

67 (49.3 - 91.2) mg/kg for males
58 (44.3 - 76.0) mg/kg for females

The toxic symptoms developed in two to four hours and deaths resulted in 24 hours. The symptoms included tremor, clonic convulsions, and hind limb or whole body ataxia. Necropsy was reported as being unremarkable.

The study is CORE MINIMUM. The results of the clinical observations and necropsy are reported in narrative form without supporting data. Mice are not a usual species for LD_{50} determinations.

Acute Oral Toxicity of S-3206 in Rabbits

Sumitomo Chem. Co., FT-00-0039, September 12, 1980
EPA Accession No. 249937, Tab IV-A-4

8 groups of 5 male and 5 female albino rabbits (Japanese strain) were dosed with either 0, 89, 133, 200, 300, 450, 675, or 1000 mg/kg of test material (S-3206, lot # 90403, purity 96.2%) and observed for mortality and reactions for 14 days. The test material was dissolved in corn oil. The following LD_{50}'s with 95% confidence limits were determined.

675 (504 - 905) mg/kg for males
510 (300 - 867) mg/kg for females

The rabbits which died died within 1 (usually) to 2 days but as late as 4 days. The toxic signs included muscular fibrillation, tremor, whole body ataxia, slow respiration and diarrhea developed at 133 mg/kg and above, the symptoms were reported as disappearing after 4 days. No changes in body weight or dose related macroscropic lesions were reported.

This study is CORE MINIMUM. Rabbits are not a usual choice for acute oral LD_{50} determinations.

Oral Dose Range Finding Study in Dogs S-3206

Hazleton Labs. 343-123, Oct. 11, 1979
EPA Accession No. 249937, Tab IV-A-5

3 groups of 2 male and 2 female beagle dogs were dosed with either 1000, 464, or 100 mg/kg of test material (S-3206, lot # 90403 reported to be 96.2% pure), in a gelatin capsule. A fourth group of 1 male and 1 female received gelatin capsules of 46 mg/kg. A fifth group received a diet of 4000 ppm for four days and later 2000 ppm for eight days. The dogs were observed for 14 days before sacrifice.

A single dog receiving the 1000 mg/kg capsule died. The LD_{50} was not determined but is greater than 1000 mg/kg (single dose). The toxic symptoms included food emesis, slight salivation, poor pupillary response, tremors and decreased activity.

The dog dosed with 4000 ppm of S-3206 developed emesis and had mucoid blood or blood mixed with mucoid feces. At 2000 ppm the dogs exhibited slight tremors, some ataxia and decreased locomotor activity. Some changes in body weight and reduced feed consumption were noted. Necropsy was unremarkable.

This study is CORE SUPPLEMENTARY. No firm LD_{50} in dogs was determined. It is >1000 mg/kg. The dogs would not tolerate 4000 ppm in the diet.

Acute Oral Toxicity of Two Impurities of S-3206 (Technical) in Mice

Sumitomo Chem. Co., FT-00-0044, Feb. 1981
EPA Accession No. 249937, Tab IV-A-6

The impurities of S-2306 described as [redacted] were assessed for their acute oral toxicity. The samples were dissolved in corn oil and (three groups of 10 male and 10 female mice) were dosed at 0, 2500 and 5000 mg/kg. (Note the compounds were stated as being 99.5% and 97.2% pure.) Mice were observed for 14 days.

No mice died. The LD_{50}'s are greater than 5000 mg/kg for these chemicals. Only some signs of decreased activity were noted. Body weights were unaffected and there were no microscopic lesions due to the test chemicals reported.

This study is MINIMUM. The test concerns impurities of the technical material.

Acute Oral Toxicity of 2,2,3,3-tetramethylcyclopropane Carboxylic Anhydride in Mice ← Carswell #842D

Sumitomo Chem. Co., FT-90-0045, Feb. 1981
EPA Accession No. 249937, Tab IV-A-7

Eight groups of 7-week old mice (10 males and 10 females) were fasted and dosed with either 0, 500, 750, 1000, 1300, 1700, 2200, or 2500 mg/kg of test material (2,2,3,3-tetramethylcyclopropane carboxylic anhydride, stated to be 99% pure) dissolved in corn oil and observed for 14 days. The following LD_{50}'s with 95% confidence intervals were determined:

1450 (1280 - 1630) mg/kg for males
1880 (1450 - 2430) mg/kg for females

The signs of intoxication were reported to be decrease in spontaneous activity, ataxia, limb paralysis, irregular respiration, hyperpnea, dyspnea, pilperection and incontinence were noted at dose levels of 500 mg/kg and above. Deaths occurred at 1000 mg/kg and above. Body weight was reduced in the group receiving 1300 mg/kg. Necropsy was reported as being unremarkable.

The study is MINIMUM. The test concerns impurities of the technical material.

Intravenous Toxicity of SD-41706 (S-3206) or (1-24-0-0) in the Mouse

Laboratory and Date not provided, study is No. TIR-74-110-76
EPA Accession No. 249937, Tab IV-A-8

The following is a direct quote from the abstract of the study provided:

> "The intravenous LD_{50} value of SD 41706 (1-24-0-0) was calculated to be 4.5 (3.9-5.3) mg/kg. The onset of toxic effects was rapid (within seconds). Time of recovery and lethality was within minutes. Toxic signs noted were generalized tremors followed by clonic and clonic-tonic (forelimb flexor) convulsions and death, presumably from respirator failure. (TIR-74-110-76)"

This study is considered INVALID in the absence of information on where and when the study was conducted. The test material is not identified as other than SD-41706, (1-24-0-0).

Acute Subcutaneous and Intraperitoneal Toxicity of S-3206 Technical in Rats and Mice

Sumitomo Chem. Co., FT-60-0037, July 19, 1976
EPA Accession No. 249937, Tab IV-A-9

Groups of 10 male and 10 female 8-week old rats (Sprague-Dawley) and 7-week old mice (dd) were dosed with test material (S-3206, lot #022108 of 97.0% purity as reported) by both the subcutaneous and intraperitoneal routes and observed for 14 days. The following LD_{50}'s with 95% confidence intervals were determined.

In rats

1,410 (1,146-1,734) mg/kg for males - subcutaneous toxicity
900 (789-1,026) mg/kg for females - subcutaneous toxicity

225 (192-264) mg/kg for males - intraperitoneal toxicity
180 (158-205) mg/kg for females - intraperitoneal toxicity

In mice

1,350 (992-1,836) mg/kg for males - subcutaneous toxicity
900 (662-1,224) mg/kg for females - subcutaneous toxicity

230 (193-274) mg/kg for males intraperitoneal toxicity
210 (177-249) mg/kg for females intraperitoneal toxicity

Symptoms similar to those described by the oral route were reported. No other changes were noted at necropsy

(except direct injury due to subcutaneous injection). This study is MINIMUM. Subcutaneous and intraperitoneal routes are not usual routes of study for acute toxicity.

Acute Dermal Toxicity of S-3206 in Rats

Institute for Biological Sciences, Sumitomo Chem. Co., FT-60-0019, January 1979 EPA Accession No. 249937, Tab IV-A-10

Seven groups of 20 rats (10 males and 10 females) were prepared by clipping (but no reference is made to abrading) and dosed with either 100, 250, 500, 750, 1000, 2500 or 5000 mg/kg of test material S-3206, 97% pure lot #022018) dissolved in corn oil. The test material was covered with surgical tape and kept in place for 24 hours. After removal of the tape the rats were observed for 2 weeks.

LD_{50}'s of (with 95% confidence limits) were determined:

1,600 (1,150-2,220) mg/kg for males
870 (670-1,120) mg/kg for females

The minimum toxic dose was reported to be 250 mg/kg for both sexes. Signs of intoxication included hypersensitivity, tremor, incontinence of urine, hind limb ataxia. Deaths occurred within 3 days and the rats were reported as being normal within 12 days. Necropsy was reported as unremarkable.

This study is MINIMUM. The data are in narrative form. Rats are not the usual choice for acute dermal LD_{50} studies.

Acute Dermal Toxicity of S-3206 Technical in Mice

Sumitomo Chem. Co., FT-60-0036, August, 1980
EPA Accession No. 249937, Tab IO-A-11

Seven groups of 20 (10 male and 10 female) mice (six weeks old) were prepared by clipping (no reference was made to abrading) and dosed with either 100, 300, 600, 1000, 1750, 2500 or 5000 mg/kg of the test material (S-3206, 97% pure, from lot 022018) dissolved in corn oil. The test material was kept in place for 24 hours with surgical tape. After removal, the mice were observed for 2 weeks. LD_{50}'s with 95% confidence intervals of

740 (587-932) mg/kg for males
920 (676-1,251) mg/kg for females

were determined.

The minimum toxic dose was reported to be 300 mg/kg in both sexes. The toxic signs included hypersensitivity, tremor, incontinence, and hind limb ataxia. Deaths occurred within 3 days and the surviving mice were reported normal after 5-12 days. Autopsy was reported as unremarkable.

This study is MINIMUM. The data for observations and necropsy are in narrative form. Mice are not the usual choice for acute dermal LD_{50} studies.

S-3206 Technical Grade Acute Dermal Toxicity (LD_{50}) Study in Rabbits (TSCA 7/79) (EPA 8/78) (OSHA)

IRDC,#491-002, October 26, 1981
EPA Accession No. 249937, Tab IV-A-12

A single group of 10 rabbits (New Zealand white, 5 males and 5 females) was dosed with 2000 mg/kg of test material (S-3206, technical grade, the % purity was not stated) and the test material was kept in place for 24 hours. The rabbits were prepared by both clipping and abrading. Two untreated rabbits were clipped and abraded and served as controls.

No rabbits died. Six of the rabbits were reported as being normal and not having adverse reactions. The other rabbits exhibited soft stool and purulent nasal discharge. No macroscopic or miroscopic lesions attributable to the test chemical were noted. The skin reaction (at the site of application) was described as "very slight erythema" or "very slight edema."

This study is CORE MINIMUM. Technical S-3206 is Tox Cat III by the dermal route of exposure.

Acute Inhalation Toxicity of S-3206 and S-5602 in Mice and Rats

Institute for Biological Sciences, Japan AT-50-0043, Aug., 1976
EPA Accession No. 249937, Tab IV-A-13

Note: This study was conducted with both S-3206 (fenpropathrin) and S-5602, but in this review only information concerning S-3206 is being considered. No information was available in this report on the identity of S-5602.

For this study, an atmosphere containing S-3206 was generated by injecting a constant rate of test material into an atomizer and sprayed under compressed air. The mist produced was passed through two bottles (in series) to remove large sized particles (the contents of the bottles were not stated). The atmospheric concentration was determined by trapping the mists in a "finely powdered silicagel" located in the sampling line (a line apparently taking the atmosphere

from the center of the chamber), and later analyzing the trapped compound gas chromatographically.

The test sample used for this study was 20 gm of S-3206 of 97.0% purity (lot #022018). It was prepared as a formulation with 10 gm of Sorpol 3005X diluted to 100 ml with xylene. Exposure time was for 3 hours.

Part 1 - Rats

Six groups of 8 male and 8 female rats were exposed to atmospheric concentrations of 0, 4.5, 12.0, 24.0, 48.0, or 96.0 mg/m^3 of S-3206. No rats died. Responses to the exposure included salivation, incontinence of urine, lacrimation, tremor, hyperergia (excited state), and abnormal respiration. The lowest test dose level which showed signs of intoxication was 24.0 mg/m^3. Necropsy was unremarkable.

Part 2 - Mice

Six groups of 10 male and 10 female mice were exposed as above. LC_{50} values were determined to be 100 mg/m^3 for male mice and 43 mg/m^3 for female mice. The onset of symptoms of intoxication (see under the rat study above) was observed 30 to 60 minutes after initiation of exposure. Some symptoms at the higher exposure levels persisted for 24 to 48 hours. In the mouse study ataxia preceded deaths. Necropsy was unremarkable.

This study is CORE SUPPLEMENTARY. The data establish that fenpropathrin as formulated is quite toxic by the inhalation route. The LC_{50} in mice (females) is 43 ug/L. Tox Cat I is <0.2 mg/L. No LC_{50} was established for rats although no rats died at an exposure level of 0.096 mg/L. The description of the procedure for generating the atmosphere is vague: no description of the material in the glass bottles used to trap the large particles was provided. The test material used is not identified as a formulation for which registration is sought.

Primary Eye and Skin Irritation Test of S-3206 in Rabbits

Sumitomo Chem. Co., ET-80-0023, January 1979
EPA Accession No. 249937, Tab IV-A-14

Part A. Eye Irritation

0.1 ml of test material (S-3206, lot AM-212, 90.2% purity) was instilled into the everted lower lid of one eye of each of 9 rabbits. The eyes of 3 of these rabbits were washed with lukewarm water 30 seconds after application.

No corneal opacity developed. Irritation of the iris and conjunctivae receded before 72 hours. Some hyperemia of the conjunctivae developed.

This study is CORE GUIDELINES. Tox Cat III is supported.

Part B. Dermal Irritation

Six rabbits were prepared by clipping and abrading (18G needle) and dosed with 0.5 ml of test material (same as part A above) and the material was kept in place for 24 hours.

A primary irritation score (PIS) of 0.0 was determined.

This study is CORE GUIDELINES. The technical S-3206 may be classified as Tox Cat IV based on dermal irritation.

Skin Sensitization Study of S-3206 in Guinea Pigs

Sumitomo Chem. Co., FT-50-0024, July, 1979
EPA Accession No. 249937, Tab IV-A-15

Groups of Hartley strain male guinea pigs were prepared by clipping and dosed intracutaneously with test material (S-3206, lot #022018, purity 97.0%) at 1% and 5% in corn oil solutions (8 guinea pigs per group). A positive control group (5 pigs) was dosed with 0.05% dinitrochlorobenzene. The pigs were sensitized with S-3206 10 times or 3 times weekly. The dose level was 0.05 ml the first day and 0.10 ml for the subsequent injections. The challenge application of 0.05 ml was conducted 14 days after the last sensitization administration.

No signs of a sensitization reaction to S-3206 were reported as developing. The positive control gave the expected positive result.

This study is CORE MINIMUM. S-3206 is not a sensitizer under the conditions of this experiment using guinea pigs as test animals.

Skin Sensitization Test of S-3206 in Guinea Pigs

Sumitomo Chem. Co., FT-10-0078, October 26, 1981
EPA Accession No. 249937, Tab IV-A-16

Note: This study using Buehler's method of application of the test material by a patch was conducted because the method of intracutaneous application could only use very dilute (1.0% and 5.0%) preparations of S-3206.

Four groups of Hartley strain male guinea pigs were prepared by clipping and dosed with test material (S-3206, lot #00705, purity 88.1%, a brownish solid) diluted 2 times with acetone by applying the acetone mixture to a lint patch and taping the patch to the prepared area of the skin. The sensitization

or induction was performed 3 times a week for a total of 10 applications. Two weeks after the last application each guinea pig was challenged in the same manner as the sensitization application. 2,4-dinitrochlorobenzene was applied to a group of guinea pigs to serve as a positive control.

No signs of a sensitization reaction developed in the guinea pigs treated with S-3206. The positive control group developed the expected positive response.

This study is CORE MINIMUM. S-3206 is shown by this study in guinea pigs not to produce a sensitization reaction.

Toxicity of Pyrethroid Insecticides: Investigation of the Neurotoxic Potential of WL 41706 (S-3206) to Adult Hens

Shell Research Ltd., TLGR-0068.77, August 1977.
EPA Accession No. 239937, Tab IV-A-17

Three groups of six adult hens were dosed as either negative control, positive control or with S-3206 test material. The S-3206 test group was dosed with five successive daily doses of the test material, designated as WL-41706 batch #13, of 96% purity at 1 gm/kg/day. The positive control group received a dose of 0.5 ml/kg of TOTP (tri-o-tolyl phosphate) after first being pretreated with atropine and pralidoxime. The group receiving S-3206 was redosed after 3 weeks and then was sacrificed 3 weeks after the second dose.

No signs of ataxia or histological evidence of nerve damage were reported in the hens dosed with S-3206. The positive control group produced the expected ataxia and axonal damage.

This study is CORE MINIMUM. S-3206 is shown not to produce delayed neurotoxic response in hens in this study.

WL-41706 (S-3206) - A Short-Term Feeding Study in Rats

Shell Research Ltd., TLGR 0041.76, June, 1976
EPA Accession No. 239937, Tab IV-B-1

Two groups of 6 male and 6 female Charles River (UK) rats (from Manston Kent) were dosed with diets containing either 0 or 900 ppm of test material (WL-41706, batch 24 supplied by the Shell Woodstock Laboratory). The investigations made for this study were limited to "general health and behavior, followed by gross pathological examination." Sections of the sciatic nerve were reported to be stained by the cresyl violet-luxol fast blue method for myelin and by the Glees and Marsland method for axons and then examined histologically.

Results

All of the six females died by day 5 as a result of the presence of the test chemical in the diet. The onset of tremors began as early as day 1. Four of the 6 males died on day 16 and day 20. The males showed tremors which progressed to violent and erratic jumping.-

The report states that the rats displayed "swelling and disintegration of nerve axons, in some cases apparently involving every fiber in all except one of the 12 animals receiving a dietary concentration of 900 ppm even in those whose survival time is very short. No definite myelin lesion can be seen and the nerves from the control animals are normal."

Conclusion: The study established that rats dosed with 900 ppm of fenpropathrin (WL-41706) develop axonal swelling and disintegration. No NOEL for this lesion was established. This test dose level (900 ppm) is also fatal (within 5 days) to female rats. This study is CORE SUPPLEMENTARY. The study cannot be used as a subchronic feeding study.

Toxicity Studies on the Insecticide WL-41706 (S-3206): A Three-Month Feeding Study in Rats

Shell Research Ltd. UK., TLGR. 0020.76, date of report: December 12, 1979, EPA Accession No. 249937, Tab IV-B-3

Five groups of 12 male and 12 female rats (Charles River, supplied by Manston, Kent) were dosed at either 3, 30, 100, 300 or 600 ppm of test material. The control group consisted of 24 male and 24 female rats. The high dose group receiving 600 ppm was included after the plans for the experiment were made and the animals in this group were not randomized in the same way as the other groups. Thus, the group receiving 600 ppm was handled separately from the other groups receiving the test material, but this group was compared with the control group. For example, statistical evaluations for the 600 ppm group were usually compared with the groups receiving lower dose levels.

Results:

Survival: All rats survived the 90-day feeding period.

Body Weight: Only the female group receiving 600 ppm was reduced in body weight.

Clinical signs: Were noted only in the group receiving 600 ppm, but in this group the tremors noted occurred at week 5 and were reported to have disappeared by week 11.

Hematology (samples taken at termination only and included evaluations on packed cell volume, red and white cell counts, hemoglobin, the prothrombin and kaolin-cephalin coagulation times). The packed cell volume was reported to be depressed 2-5% in males and females at 300 ppm, but no difference was noted at 600 ppm (at best only 2%). At 600 ppm there were reported some "minor" reductions in Hb (3% both sexes) and mean cell volume (2% both sexes). There was also noted a "small increase" in the prothrombin time in males (2%) and a small decrease in kaolin-cephalin clotting time (14%) in females at 600 ppm.

A NOEL of 300 ppm is set for effects on blood parameters. At 600 ppm the kaolin-cephalin clotting time is considered to be decreased as a result of the presence of the test material.

Clinical chemistry (samples were taken at termination only and included observations on protein, urea, alkaline phosphatase, plasma glutamic pyruvic transaminase, plasma glutamic oxalacetic transaminase, K^+ and Cl^-).

Plasma urea was elevated in females dosed with 100 ppm (13%), 300 ppm (16%) and 600 ppm (10%). Males were not increased but the group receiving 600 ppm was depressed (-10%). The report discounted the effect on urea as being a toxic response to the test material because the results for all doses were within the range reported for the strain of rat used. Toxicology Branch concurs.

At 600 ppm there was noted an increase in plasma alkaline phosphatase in both males and females (33% for males and 42% for females). The lower-dosed groups did not reach statistical significance except for the female group receiving 3 ppm (58% increase). The testing laboratory considered that the increases noted at 600 ppm were a response to the test material.

The serum K^+ level was elevated in the male group receiving 600 ppm (+10%) and the Cl^- level was decreased in the female group (2%).

A NOEL for changes in clinical chemistry is conservatively set at 300 ppm. At 600 ppm there is noted a possible increase in alkaline phosphatase.

Organ Weights: The heart, brain, liver, spleen, kidneys, and testes were weighed. The only statistically significant difference noted in the rats dosed with 300 ppm or less was an increase in female relative liver weight for the 300 ppm test group (+7.2%). This increase in liver weight was not evident in the female rats dosed with 600 ppm. However, the rats dosed with 600 ppm showed increases in kidney weight (males, +7.2%) and increase in brain weight (females +6.9%).

A NOEL of 300 ppm is conservatively set for effects organ weights. At 600 ppm the brain (females) and kidneys (males) weights are considered to be affected.

Urinalyses: No urinalyses were determined.

Gross Necropsy: No discussion or description of gross pathology findings were presented.

Histopathology: The rats from the controls, 100, 300 and 600 ppm dosed groups were reported to be examined histologically. The tissues reported to be examined included the brain, heart, kidney (2 sections), lung, spleen, liver, alimentary tract (5 levels), pancreas, salivary gland, thymus, mesenteric lymph node, gonads, prostate and uterus, pituitary, adrenal, larynx, thyroid, eye and sciatic nerve. The sciatic nerve was stained with both cresyl violet luxol fast blue for myelin and with Glees and Marsland stain for axis cylinders.

No individual animal pathology sheets or summary tables were presented. The results are as a list of animals and the significant lesions noted for each tissue (when a lesion was noted).

No compound related lesions (including lesions in the central and peripheral nervous systems were noted in the test rats dosed with fenpropathrin. [The pathologist responsible for reading the slides was Dr. S.T.G. Butterworth.]

CONCLUSIONS: This study is CORE MINIMUM. A NOEL of 300 ppm is supported.

A. Toxicity Studies on the Insecticide WL-41706 (S-3206): A Three-Month Feeding Study in Rats.

Shell Tunstall Lab. #TLGR. 0031.75, May 1975
EPA Acc. No. 249937, Tab. #IV-B-2

B. The test material was WL-41706 batch #13 supplied by the Shell Woodstock Lab. and was of 96% purity.

C. The test animals were male and female Carworth Farms E strain and were 5 weeks old at the start of the experiment. Groups of 12 males and 12 females were dosed with diets containing 2, 10, 50 or 250 ppm of test material. The control group consisted of 24 males and females. The rats received their test diets for 13 weeks.

D. No indications that the test diets were sampled and analyzed were presented nor was there mention of plans for the analysis in the protocol.

E. No effects on survival were noted. Body weight gain was said to be increased in the rats dosed with WL-41706 in the first weeks of this study. In males this increase was of the order of 4-5% and is not considered by TB to be of toxicological significance. Final body weights were essentially equivalent for all dose groups. Food consumption was not affected by the presence of the test material in the diet.

F. Clinical signs. No behavioral reactions to the presence of the test material were reported.

G. Hematology: Assessed at week 13 only included Hb, PCV, RBC, WBC, mean cell volume and hemoglobin, and hemoglobin concentration, prothrombin time and K.C.C.T. The only statistically significant effect noted was a decrease in RBC count (-3%). A NOEL for hematology is set at 250 ppm.

H. Clinical Chemistry. Assessed at week 13 only included protein, urea, alkaline phosphatase, SGPT, SGOT, Na^+, K^+ and Cl^-. The only effect noted was urea (increase of 9%) in the high dose group females. A NOEL is set at 250 ppm for changes in chemical chemistry. The change in urea content is not considered to be biologically meaningful.

I. Urine Analysis: No determinations were made.

J. Gross pathology: No information provided.

K. Organ weights: No consistent statistically significant dose related changes were noted in the weights of the brain, heart, liver, spleen, kidneys or testes.

L. Histopathology: Tissues were analyzed for the controls and the rats dosed with 50 and 250 ppm. Some 13 organs (plus those with obvious damage) were examined microscopically. No test chemical related affects were noted.

M. Conclusion: This study is CORE SUPPLEMENTARY. The data are in summary form only. No toxic effects were noted in the high dose test group.

A. Subchronic Toxicity in Dogs S-3206. Final Report

Hazleton Laboratories, (#343-125) and Sumitomo #FT-01-0034
July 17, 1980
EPA Acc. No. 249937, TAB IV-B-4.

B. The test material used for this study was S-3206, a yellow solid said to be of 96.2% purity and was from lot #90403 and was provided by the Sumitomo Chemical Co. For the dietary preparations (in ppm), the dosages were adjusted to 100%.

C. Purebred beagle dogs bred by Hazleton Research Animals were used for this study. There were 4 groups of 6 males and

6 females per dosing group, including the controls. The dogs were dosed with either 0, 250, 500 or 750 ppm of S-3206 in their food for 13 weeks. The high dose group received 1000 ppm for weeks 1-3 and the lower level of 750 ppm for weeks 4-13.

D. The test diets were prepared weekly and samples were sent to the sponsor for analysis. No report of the analysis of the test diets was included in the study report.

E. Mortalities: A single dog receiving the 1000 ppm diet was sacrificed in a moribund state during the 3rd week of the study. This dog showed severe tremors and other signs of poisoning. Its death was determined to be related to the test material. Thus, the high dose test group was changed to 750 ppm. Several types of signs of reaction to the test material were noted; these included soft and mucoid stools, and/or diarrhea, emesis, tremors, and ataxia, sometimes, lethargy, panting and salivation.

The data presenting the clinical findings are in an addendum found in TAB IV-B-5. These tables show that there are increases in emesis and the passage of soft, mucoid stools or diarrhea, at the lowest test dose level. See the following table:

	Males		Females	
	Stools*	Emesis	Stools*	Emesis
Controls	24	2	16	5
Low (250 ppm)	34	10	66	9
Mid (500 ppm)	40	25	25	10
High (750 ppm)	34	19	36	25

*Stools - refers to incidences when the stool was reported as soft, mucoid or there was evidence of diarrhea. Note: the high dose male group had one less dog for most of the study.

With respect to tremors, the total incidences reported for males were 0, 2, 5, and 94 and for females were 0, 2, 3 and 149 - for the controls, low, mid and high dose test groups respectively. For both the males and females only a single dog was affected in the low dose group and this was in the first 2 or 3 weeks of the study.

A true NOEL for effects on the gastrointestinal system is <250 ppm.

A NOEL for tremors is set by TB to be 250 ppm, the few incidences noted at this level are considered to be of insufficient

magnitude to assign a NOEL of <250 ppm.

F. Body weight gain. The report states that the high dose group males and females did not gain weight as well as the controls and other dosed groups. For males, the high dose group was an average of 6% higher at start of the experiment, but was an average of 9% or less lower than the controls at the end. For females, the weight of the high dose group was 96% of the controls at the start, but was 90% at the end of 90 days. Thus, the high dose group is mildly affected with respect to weight gain. It appears that the mid dose group females are also slightly affected. They were 97% of the controls at the start, but were 92% at the end of 90 days of dosing.

Food consumption was not reported as being affected.

A NOEL for body weight changes (decreases) is 250 ppm.

For sections G and H below, blood samples were taken at pretest, and at weeks 5, 9 and 13. Blood was taken by jugular puncture.

G. Hematology analysis included: Hematocrit, hemoglobin, erythrocyte count, platelet count, total and differential leukocyte counts, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.

Of these parameters, the mean hematocrit, hemoglobin, and erythrocyte count of both high dose males and females were depressed and thus was considered to be compound related. The magnitude of these depressions was 9% (females, hematocrit), 11% (male hemoglobin) and 13% (females, RBC count).

A NOEL for changes in the blood particularly decreases in hematocrit, hemoglobin and RBC(count) is 500 ppm.

H. Clinical chemistry parameters measured included: total protein, albumin, alkaline phosphatase, total bilirubin, BUN, total cholesterol, Cl^-, lactic acid dehydrogenase, fasting glucose, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, total globulin, albumin/globulin ratio, K^+, Na^+ and Ca^{++}.

Of these parameters, some possible effects were noted with respect to decreases in SGOT (among females, 25%), Ca^{++} (among males, 5%), and Na^+ (males, up to 5%). TB does not consider that the magnitude or consistency of the changes in these parameters to be a definite dose induced affect.

A NOEL of 750 ppm is assigned for changes in blood chemistries.

I. Urinalysis: (Tests were made at predosing and at 13 weeks.) The parameters investigated included: appearance, pH, specific

gravity, glucose, ketones, total protein, bilirubin, occult blood, urobilinogen, reducing substances, and microscopic examination of the sediment.

No test chemical effect on any of these parameters was noted. A NOEL of 750 ppm is assigned for urinalyses.

J. Gross Necropsy. Following 13 weeks of dosing the surviving dogs were sacrificed with a dose of sodium thiamylal and a necropsy was performed. A NOEL for gross necropsy lesions is set at 750 ppm. There were no compound related lesions noted in the dogs sacrificed at 13 weeks.

K. Organ weights: The pituitary, thyroid, adrenals, brain, lungs, heart, liver, spleen, kidney and testes were weighed at termination. No dose related or compound related effects were noted. The mid dose female group liver weight was elevated (9%) but the high dose group was 4% lower than the controls. Although pyrethroid type chemicals cause changes in liver weight (elevation), no compound related effect was noted for this study.

NOEL for organ weight changes is 750 ppm.

L. Histopathology. Some 32 tissue types were routinely prepared and examined histologically.

A NOEL for microscopic findings is set at 750 ppm. No signs of lesions that were related to test material were noted.

M. Ophthalmologic examinations were performed initially and at termination. No test chemical effects were noted.

N. Conclusion: Core classification of this study is MINIMUM. The NOEL for this study is <250 ppm.

Effects of the test material at 250 ppm on the gastrointestinal system are noted by TB but because of the nature of this effect a second study is not required at this time. The dog chronic feeding study should be designed and conducted to determine the NOEL. At 500 ppm there is noted weight loss and body tremors (occasionally tremors were noted at 250 ppm), at 750 ppm there is increased weight loss, more intense tremors and ataxia, and blood changes in the RBCs.

The effects of feeding WL-41706 (S-3206) on the microsomal mono-oxygenase system of rat liver.

Shell Tunstall Laboratory #TLGR 0043.76, July 1976
EPA. Acc. No. 249937, TAB IV-B-7.

This study was conducted to assess the ability of WL-41706 (fenpropathrin) to induce the microsomal mono-oxygenase system of rat liver. For example, the study was run to determine if high levels of WL-41706 in the diet cause an induction of more enzyme to be produced in the liver.

5 groups of 4 male rats were fed diets containing either 0, 1.0, 10.0, 100.0 or 1000 ppm of WL-41706 (Batch 266, 97% pure), a positive control group consisting of 2 male rats were fed 100 ppm of dieldrin. After two weeks of feeding, the rats were sacrificed and their liver hemogenates were prepared. The specific activity of the microsomal mono-oxygenase system of rat liver was determined by measuring the rate of O-de-ethylation of [^{14}C] chlorfenvirphos in vitro.

Results. No clear effect of feeding WL-41706 in body weight gain or liver relative or absolute weight was evident. The positive control rats (dieldrin) had no evident changes in body weight but liver weights both absolute (+59%) and relative (+ 54%) were increased.

The specific activity for O-de-ethylase was not clearly affected by treatment with WL-41706. The high dose group (1000 ppm) was elevated only slightly. The activity for the enzyme derived from the dieldrin treated rats was elevated 16 fold. Thus, feeding high doses of WL-41706 did not induce the hepatic mono-oxygenase system. It should be noted that some compounds which have a very high and rapid metabolism by the mono-oxygenase system do not induce this system to produce more enzyme (see study introduction for discussion).

This study is ACCEPTABLE.

A. S-3206 (Technical Grade) 21-day dermal toxicity study in rabbits

IRDC, #491-010, Jan. 22, 1982, EPA Acc. No. 249937, Tab. IV-B-8.

B. The test material used for this study was S-3206 T-G, it was from lot no. 01113 and was of 91.4% purity and supplied by the Sumitomo Chem. Co. Osaka, Japan.

C. The test animals were New Zealand white rabbits. They were prepared for dosing by both clipping and abrading. There were 10 rabbits of each sex per group, five were clipped only and had intact skin and 5 were clipped and the skin was further abraded. Note: There was a sexing error in the low dose group so that there were 9 males and 11 females in this group. The dose levels selected were 0, 500, 1200, 3000 mg/kg of S-3206. The test material was premoistured with normal saline and evenly distributed over the rabbits backs. The group receiving the highest dose level had 15-20% of

their body surface covered with the test material. Lower doses had proportionally lesser amounts of their body surface covered. After application, the treated areas (including, the test material) were covered and overwrapped with elastoplast plastic tape. The rabbits were further restrained by collars to prevent ingestion of the test material. The test material was kept in contact with the rabbit for 6 hours. Dosing was repeated once daily, five days per weeks, for three consecutive weeks (total of 15 doses per rabbit). After 21 days, the rabbits were sacrificed.

D. Dietary analysis - N/A.

E. Survival behavioral reactions and dermal reactions. A single rabbit died, but no cause of death was noted. This rabbit was in the group receiving 500 mg/kg (a male). Thus, no effect of increased mortality was related to the test material. No behavioral or clinical signs were noted.

Only one rabbit in each of the groups receiving 500 mg/kg and 1200 mg/kg had "doubtful or barely perceptible erythema." The rabbits receiving 3000 mg/kg had many instances of "doubtful or barely perceptible erythema" and edema. No moderate or severe cases were reported.

F. Body weight and food consumption. No consistent dose related changes in body weight gains were noted. After 21 days of dosing the males in the high dose group were 98 gms (average weights) larger than the controls, the high dose group females were 35 gms (average weights) lower than the controls. No differences in food consumption were noted.

For sections G and H below, 35 rabbits/sex were assessed during the predosing period and 5 rabbits/sex/dose group were assessed at the study termination. Blood was obtained via puncture of the main ear artery from rabbits fasted overnight.

G. Hematology - determinations included hemoglobin, hematocrit, total erythrocyte count, total and differential leucocyte counts, platelet counts and reticulocyte counts. Mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and concentration were calculated.

TB noted that leucocyte counts for all dosed groups were down (36% to 28%) but no dose response was noted and females were not affected, therefore this effect is not considered by TB to be related to the test material.

The other parameters were equivalent to the controls.

H. Clinical biochemical assessments were conducted for glucose, BUN, aspartate aminotransferase, alkaline phosphatase, alanine aminotransferase, total protein, albumin, globulin,

Ca^{++}, cholesterol, total bilirubin, creatinine, lactic dehydrogenase, Na^{+}, K^{+}, Cl^{-} and phosphorous.

Among the male groups, deviations from the controls were noted for globulin, lactic dehydrogenase (decrease) and alkaline phosphatase (increase). Among the females deviations were noted for lactic dehydrogenase (decrease), SGOT (decrease) and alkaline phosphatase (increase). None of these changes are considered by TB to be of sufficient magnitude or consistency to be of toxicological concern.

I. No urinalyses were made.

J. Gross necropsy. All rabbits received an external and internal necropsy including palpation. No compound related lesions were noted.

K. Organ weights. The liver, kidneys, heart, pituitary, gonads, thyroid (parathyroid) and adrenals were weighed. There were no consistent statistically significant dose related weight changes for these organs noted.

L. Histopathology. Histopathology was routinely performed for the skin (treated and untreated areas, 3 sections each), the liver and the kidney plus any other tissues which had evidence of an obvious lesion. Some 25 other tissues and organs from the rabbits were removed and preserved for future microscopic examination (if necessary).

Trace or mild "inflammatory cell infiltration" in the intact and abraded skin was reported as being observed among males and females receiving 0, 500, 1200, and 3000 mg/kg. This effect was the only lesion type that was attributable to the test material. The liver and kidney were not reported as displaying reactions to the test material.

Conclusion. This study is CORE GUIDELINES. Dermal dosing at dose levels as high as 3000 mg/kg for 21 days (15 doses) did not result in signs of systemic toxicity. Only signs of mild local irritation resulted.

A. Toxicity studies on the insecticide WL 41706 (S-3206): A three generation reproduction study (minus histopathology) in rats.

Shell Research Laboratories, #TLGR. 79,071, June 1979
EPA Acc. No. 249938, Tab. IV-C-6.

B. The test material used for this study was WL-41706, batch no. 26C, 97% pure and was supplied by the Shell Biosciences Laboratory.

C. The test animals were supplied by the Charles River Co. (France) and were COBS strain. The experimental design

consisted of 4 groups (basically 30 females and 30 males) dosed with either 0, 5, 25 or 250 ppm of WL-41706 in the diet. The original parental generation produced F_1A and F_1B generations. The F_1B groups were culled to 30 males and 30 females per group and produced F_2A and F_2B generations. Similarly, the F_2B group was culled to produce the F_3A and F_3B generations.

D. Data were provided which showed that the test diets contained levels of WL-41706 at very near the desired levels of 5, 25, or 250 ppm. The data also showed that the test material was stable in the diet for 5 1/2 weeks.

E. Effects in mature rats. There were no obvious reactions to the test material noted in the mature rats. Body weight was not consistently affected. It was noted that as the study progressed to the third generations, there were in all groups including the controls (i) matings not resulting in pregnancy, (ii) single sex litters, (iii) pups not surviving to weaning, but there was no indication that these changes were related to the test material in the diet. The gestation index, viability index and lactation index were not affected as the experiment progressed and did not show signs of being dependent upon the test material in the diet.

F. Effects on the pups. Some inconsistencies in body weight were noted. For example, all dosed pups had increases in body weight for the F_1A generation (as much as 11%). The F_1B generation was also slightly higher in some cases (4%, females only). The F_2A and F_2B generations did not display increases or decreases in pup weight that were statistically significant. The F_3A generation high dose group males (-11%) and females (-10%) showed decreases in pup weight. For the F_3A generation mid dose level the males (-5%) and females (-7%) were also lower [note pups were weighed at weaning].

TB conservatively sets a NOEL for changes in pup weight at 25 ppm.

No other effects on the pups were considered to be of toxicological concern.

G. Gross Pathology (all surviving F_0, F_1, F_2 parents were examined). No definite test chemical related lesions were noted in the parental generations. A single male and female pup from each litter of the F_3B generation (after weaning) was also subjected to gross necropsy. No test chemical related lesions were noted.

Note: 10 male and 10 female rats from the F_0, F_1, and F_2 parental groups were also prepared for histopathology. The histopathology report was not presented (as of October 1983).

Conclusion: CORE classification of this study is CORE MINIMUM. A NOEL of 25 ppm is supported; at 250 ppm there is evidence of body weight gain effects in the F_3A generation (decreases).

Teratology Study in Rats S-3206 - Final Report

Hazleton Laboratories America, Inc. USA.
#343-122, April 22, 1980.
EPA Accesion No. 249930, Tab IV-c-4.

1. The test material used for this study was S-3206 technical (Lot #90403) and was stated as being 96.2% pure. For the purpose of dosing, the test material was adjusted to 100%.

2. The test animals were Fischer 344 strain (CD®F) rats obtained from the Microbiological Associates, Walkerville, MD. For the main study, four groups of mated females were dosed with either 0 (27 rats), 0.4 mg/kg (27 rats), 2.0 mg/kg (28 rats) or 10.0 mg/kg (28 rats) of test material in corn oil. The test material was administered by oral intubation from day 6 through day 15 of gestation. On day 19 of gestation the females were sacrificed by CO_2 asphyxiation and the fetuses and dams were examined.

Note: a pilot study revealed that no signs of toxicity were observed in rats dosed with 0.5 or 2.5 mg/kg of S-3206. However, rats dosed with 12.5 mg/kg died but deaths were thought to be due to a preparation error (faulty mixing) and a second group dosed with 12.5 mg/kg showed only signs of nervous system excitation. Thus, the dose level of 10.0 mg/kg was selected as the high dose test group.

3. Observations in the dams - one mid dose and nine high dose group females died during the treatment period. There were no deaths in either the control or low dose groups. The cause of death or incidences of physical signs prior to death was not reported (other than blood around the eyes and red eyes). The high dose group gained weight at a lower rate during treatment, but this rate was higher following treatment when compared to the controls. Total body weight change for the high dose test group was comparable to the control group. There was also noted some reduction in food consumption among the treated rats. The NOEL for chemical effects in the dams is set at 0.4 mg/kg, at higher levels deaths result.

4. Gross pathology of the dams - Several gross lesions were noted in the dams which were found dead during the study. These included lungs which were dark red and/or spotted, several other major organs were also dark or red in color and other changes in organ structure were noted. The surviving rats (except one which had a nodule in the left inguinal area) did not have remarkable gross lesions.

5. Pregnancy rate and other in utero data. The pregnancy rate was 85%, 89%, 86% and 75% for the control, low, mid and high dose test groups, respectively. The low rate for the high dose group is independent of the test compound. The implantation efficiency (implantations/corpora lutea) was comparable for all groups.

No meaningful differences were noted for the incidences of resorptions, or fetal viability. One litter of 9 pups in the high dose test group was listed as dead in the summary table (p.35) but not in the report discussion.

6. Fetal data - general. No differences (of significant magnitude) were noted in fetal weight or crown-rump distance although the high dose group, both males and females, showed a lower weight and distance (2-4%). The mean sex ratio was 1.69 to 1.94 for all groups without showing a relationship to the presence of S-3206.

7. Fetal visceral examination. Approximately one-third of the fetuses (65, 76, 66 and 45 pups for the control, low, mid and high dose test groups, respectively) were fixed in Bouin's solution and sectioned by Wilson's freehand technique and examined. No visceral abnormalities were noted except in the two dead fetuses (one control and one mid dose group). No comments were made regarding the 9 dead fetuses in the high dose test group.

8. Fetal skeletal examination. A group of 8 fetuses from the same litter in the high dose test group displayed lagging ossification. This was said to be the result of possible delayed implantation. No other indications of skeletal effects were noted. This effect is not considered to be related to the test material by Toxicology Branch. Skeletal examination was evaluated for the 2/3 of the pups not prepared for visceral examination.

Conclusion: This study is CORE MINIMUM. No positive control was run concurrently. The study presents a demonstration that S-3206 is not teratogenic at doses up to and including 10.0 mg/kg/day. A NOEL of 0.4 mg/kg/day is set for maternal toxicity. The LEL is 2.0 mg/kg (1 death) and a more definite effect is 10 mg/kg (9 deaths). The NOEL for fetotoxic affects is 10.0 mg/kg/day (HDT).

Toxicity of WL 41706 (S-3206) - Teratological studies in rabbits given WL 41706 orally

Shell Research Ltd. TLGR 0103.75, December, 1975.
EPA Accession No. 249938 (TAB IV-c-5).

1. The test material was WL-41706 (batch 24) containing 97% w/w alpha-cyano-3-phenoxybenzyl 2,2,3,3-tetramethylcyclopropanecarboxylate. The test material was suspended in Mazola corn oil prior to dosing.

2. The test animals were banded Dutch rabbits. These rabbits were assigned to 5 groups as control, gelatin capsule only (21 females), control gelatin capsules containing corn oil (31 rabbits), low dose group receiving 1.5 mg of test material per day (20 rabbits), mid dose group receiving 3.0 mg/kg of test material per day (21 rabbits) and the high dose group receiving 6.0 mg/kg/day (20 rabbits). The rabbits were dosed on days 6 to 18 of gestation (inclusive). On day 28 of gestation, the female rabbits were sacrificed by pentobarbitone injection and the uterine contents and living pups were examined. Note: no pilot study was run to assess the dose level selection and no positive control was included.

3. Observation in the dams. No adverse or other effects could be attributed to the test material. A total of 6 rabbits died, the causes of death were dosing injury and pneumonia. Four rabbits aborted and two of these were in the group receiving 3.0 mg/kg, but none were in the group receiving 6.0 mg/kg. No consistent statistically significant differences in weight gain were noted.

NOEL for effects on the dams >6.0 mg/kg (HDT).

4. Gross pathology of the dams - none reported.

5. Pregnancy and other in utero data. There were 18, 28, 17, 12, and 14 pregnant rabbits which survived to term for the controls, low, mid, and high dose test groups. The mid and high dose test groups appear lower but no dose response is evident. No dose related effeects on pre-implantation losses, resorptions, early fetal deaths, late fetal deaths, or total resorptions and fetal deaths were noted.

6. Fetal data general. The fetuses were delivered following Caesarian section and allowed to live for 24 hours. There were no dose related effects on the test material on the mean total number of live fetuses, sex ratio average weight, average length of the fetuses or mean percentage of fetuses surviving to 24 hours.

For sections 7 and 8 below, one third of each litter was decapitated and the heads fixed in Bouin's solution. Serial transverse sections were made to assist in gross examination of the cranial area. The remaining skeletons were prepared and stained with alizarin red.

7. Fetal visceral examination. No major or minor visceral abnormalities which could be attributed to the test material were noted.

8. Fetal skeletal examination. No major or minor skeletal abnormalities were noted which could be attributed to the test material.

Conclusion: this study is Core SUPPLEMENTARY. Little raw data or individual animal data were presented. The data are in summary tables only. There was no positive control run concurrently. The highest dose level tested did not produce a pharmacological effect in the dams. This level is only about 1/100 of the LD_{50} of fenpropathrin in rabbits. Fenpropathrin is shown not to be teratogenic at dose levels up to and including 6.0 mg/kg. A second study in rabbits will be required.

A. Toxicity studies on the insecticide WL-41706 (S-3206). 2-year chronic and oncogenicity feeding study in rats.

Shell Research Ltd. TLGR. 79.062, May 1979.
EPA Accession No. 249938, Tab IV-c-1,2,3

B. The test material used for this study was WL-41706 (S-3206, fenpropathrin) and was supplied by Shell Biosciences Laboratory. It was from batch number 26C and was 97% pure.

C. The test animals used were COBS rats supplied by Charles River (France) Ltd. The test material was administered in the diet at the dose levels of 0, 1, 5, 25, 125 and 500 ppm. The control group consisted of 72 males and 72 females. Each group receiving the test material consisted of 36 males and 36 females. Interim sacrifices of six males and six females each were scheduled at 6 months and 1 year. Thus there were 48 controls and 24 for each dosed group of each sex scheduled to receive the diet for 2 years.

D. Dietary analysis was made for the individual batches of S-3206 fortified diet. A summary table indicated that the desired dosage level was attained. Additional analysis indicated that S-3206 was stable in the diet for 5-1/2 weeks.

E. Survival: The following table illustrates the survival information for this study.

Dose Level	Males	Females
0 ppm	38(79)*	20(44)
1 ppm	18(75)	13(54)
5 ppm	16(67)	9(38)
25 ppm	19(79)	10(42)
125 ppm	17(71)	11(46)
500 ppm	16(67)	13(54)

*Number of survivors (as % of 48 for controls or 24 for the dosed rats).

Although the percentage for survival is good, the number of survivors especially for the female test groups is considerably less than the desired 25. There is no indication that the presence of the test material in the diet caused increases in death of the test animals. There were no obvious clinical signs of intoxication reported.

F. Body weight. Only sporadic decreases in the body weight of the females in the high dose test groups were reported which were not always statistically significant. Occasionally the mid dose group (125 ppm) was also decreased. Final body weight of the high dose group females was 91% of the control group and the mid dose group was 92%. A NOEL for body weight effects is set at 125 ppm.

G. Hematology. Determinations were made at 6, 12 and 24 months. The parameters investigated included Hb, PCV, RBC, WBC, mean cell volume and hemoglobin and hemoglobin concentration, prothrombin time and KCCT time.

H. Clinical Chemistry. Determinations were made at 6, 12, and 24 months. The parameters investigated included protein, urea, alkaline phosphatase, alanine and aspartate amino-transferase, Na^+, K^+, and Cl^-.

No consistent statistically significant changes were shown to be associated with the ingestion of the test material for either hematology and clinical chemistry. NOEL >500 ppm (HDT).

I. Urinalyses. No urinalyses were made.

J. Gross pathology. Gross necropsy findings are presented in a comprehensive summary table. The gross pathological examination revealed that the lungs of females had a higher rate of "subplural white foci/plaques" in the high dose test group (42% affected) when compared with the controls (only 16% affected). The other groups had 17% or less affected. The brains of females had 3 incidences of "ventral indentation-pituitary mass," the control only had a single incidence.

K. Organ weights. The brain, heart, liver, kidney, spleen, and testes were weighed at 6, 12 and 24 months. No female sex organs were weighed.

After two years, the livers of the females were statistically significantly higher for the group dosed with 125 ppm (+21.8%) and 500 ppm (+12.3%). A dose response was not evident. The male high dose group was about -2% less in weight than the controls.

The spleen weights of females were decreased (-20%) relative to the control, but the low dose group was also -15% depresssed. Because of lack of a dose response and because the spleen is a vascular organ, decrease in weight in absence of pathology is not usually considered definite of a toxic response by TB.

Female kidney weights at 12 months were lower for dosed groups (9-14%) but there was no dose response and female kidney weights were equivalent for all groups after 2 years.

Toxicology Branch concludes that there are no definite effects of the test material on organ weights shown in this study.

L. Histopathology. This aspect of the study was conducted at the Inveresk Research International (IRI), Scotland, United Kingdom. The study report is dated March 1981 and the IRI project number is 415386.

Two hematoxylin and eosin sections of each tissue were prepared, but only one section was evaluated microscopically. No list of tissues to be examined was presented in the protocol. The report presents evidence that the following tissues/organs were evaluated microscopically: liver, kidneys, lungs, heart, salivary gland, spleen, thyroids, parathyroids*, stomach, small intestine, large intestine, pancreas, lymph nodes, bladder, aorta, hock*, thymus*, adrenals, pituitary, brain, eye, skin*, bone*, muscle*, soft tissue*, peritoneal cavity*, mammary gland*, uterus/vagina, ovaries, soft tissues*, prostate, preputial gland*, testes, and seminal vesicle. [*Indicates that only a few selected samples were evaluated, apparently in response to a gross necropsy observation.]

1. Overall neoplastic response.

   a. 26 and 53 week interim kills. Only a few neoplasias were noted and there was no evidence that the dosed rats had higher incidences than the control rats when each dosed group is considered.

   b. The following table shows the neoplasia information for rats scheduled to receive the test material for 104 weeks.

	Males				Females			
	N*	Rats with Neoplasia[2]	Benign[1]	Malignant	Rats with Neoplasia	Benign	Malignant
Control	48	36	24	18	43	32	22
1 ppm	24	18	11	9	21	12	11
5 ppm	24	18	8	14	23	15	15
25 ppm	24	18	7	8	21	17	13
125 ppm	24	12	9	12	22	13	16
500 ppm	24	14	8	8	21	13	15

[Adapted from tables 9 and 10 of the histopathology report.]

* N Number of male and/or female rats scheduled for 104 weeks of dosing.

1 some rats may have more than 1 type of benign neoplasm.

2 some rats may have both benign and malignant neoplasms.

c. Individual organ discussion of neoplastic and non-neoplastic lesions. The testing laboratory asserted that there were no dose dependent or test chemical related neoplastic or nonneoplastic lesions demonstrated in this study. Inspection of the data supports this position. The following organs or tissues are discussed below for the reasons given. [Note: The pathologist responsible for evaluating the slides was R. Aitken, B.V.M.S., Ph.D. and M.R.C.V.S.]

The individual animal histopathology sheets consist of a list of tissues together with the number of sections examined. The abnormal histopathological findings are reported for each tissue. The individual animal pathology sheets do not also give information on the gross necropsy findings. Thus, it is not possible to determine if the gross necropsy observations were followed up histologically.

i. The liver. Pyrethroid type chemicals are known to cause pathological changes in rodent liver and in this study there were some changes in liver weight noted. There were 10 liver tumors noted, 3 in the

females and 7 in the males. Among the males, there were three incidences in the control group and 1 incidence in 4 of the 5 dosed groups. Among the females, there was one incidence in the control group and 2 incidences in the group receiving 125 ppm. These were described as neoplastic nodules or hepatocellular carcinomas. Nonneoplastic findings in the liver were unremarkable and consisted of lesions commonly occurring in this strain of rat.

ii. The lung. The lung has been identified as a target organ for a potential oncogenic effect for at least some pyrethroids in mice. There were no primary lung tumors reported (i.e., bronchioalveolar adenoma or carcinoma). Males displayed higher incidences of "medial muscle hypertrophy" in the test groups than in the controls. Females were not affected. The following table illustrates the data:

Incidences of medial muscle hypertrophy of the lungs

	Males		Females	
Control	5/70	(7.1)*	8/72	(11.1)*
1 ppm	3/33	(9.0)	4/34	(11.8)
5 ppm	9/32	(28.1)	2/35	(5.7)
25 ppm	7/35	(20.0)	5/35	(14.3)
125 ppm	6/34	(17.6)	4/35	(11.4)
500 ppm	10/32	(31.3)	5/34	(14.7)

*Number of incidences/rats examined () as a percent.

Starting at the 5 ppm dose level (in males) there are 3 to 4 times as many incidences of the lesion described as "medial muscle hypertrophy."

This type of lesion is not known to TB's pathologist. The registrant must clarify the nature of this lesion and provide a defense that it is not related to ingestion of the test material.

The lesion described as "subplural white foci/plaques" (see Gross Pathology, part J of this review) was not further described by histological findings in the lung.

iii. The mammary gland. Among the females there were several types of neoplasias present in the mammary gland. These included fibroadenoma, fibroma, hibernoma,

adenoacanthoma, adenocarcinoma, adenofibrosarcoma, fibrosarcoma, schwannoma (malignant) and sarcoma. The following table shows the overall distribution of these types of neoplasms in the females. Note: There was only a single incidence of an adenocarcinoma among the males (in the group receiving 125 ppm).

	Control	1	5	25	125	500
Fibroadenoma	15	6	11	11	10	7
Fibroma	0	2	0	1	0	0
Hibernoma	1	0	0	0	0	0
Adenocanthoma	1	0	0	0	0	0
Adenocarcinoma	8	4	6	4	7	7*
Adenofibrosarcoma	0	0	0	0	1	1
Fibrosarcoma	1	0	0	0	0	0
Schwannoma (mal)	0	0	0	0	1	0
Sarcoma (indet)	0	1	0	0	0	0
Number examined	30	15	18	21	20	15

*These data were shown not to be significant (P = 0.154, Fisher's one tail F statistic, TB computer).

iv. The pituitary. Neoplasms in the pituitary were very common in this study. Among the females there were 67% of the controls and 77% of the high dose group affected. Among the males 33% of the controls and 16% of the high dose group were affected. No evidence that there was an earlier development of this type of tumor in the dosed rats was presented. The following table illustrates the distribution of the pituitary neoplasms.

Pituitary Neoplasms

	Males						Females					
	0	1	5	25	125	500	0	1	5	25	125	500
Number Examined	45	21	22	22	23	19	45	22	22	20	24	22
Adenomas	7	3	3	3	4	0	18	5	5	7	7	4
Adenocarcinomas	8	5	7	6	7	3	12	10	11	10	9	13

v. Sciatic nerve. Preliminary studies (<90 days) previously conducted with S-3206 indicated that higher doses (900 ppm) may cause a type of neuropathy of sciatic nerves. The sciatic nerves for this 2 year study for the 1 year interim sacrifice were especially prepared at the Shell Laboratories and stained using HE, Luxol Fast Blue and Glees Marsland method. Only 5 rats of each sex from the control and high dose test group that were dosed for 53 weeks were evaluated microscopically following special staining. No abnormalities were reported in either the controls or dosed animals in the sciatic nerves.

No attempts to special stain the sciatic nerves of the rats dosed for 104 weeks were made. The sciatic nerves from these rats were examined histologically using HE stain, this type of stain would not detect marginal myelin or axonal abnormalities.

vi. Evidence was presented that the kidney, heart, salivary gland, spleen, thyroid, parathyroids (occasionally), stomach, small and large intestine, pancreas, lymph nodes, bladder, aorta, hock (occasionally), thymus, adrenals, brain, eye, skin, bone, muscle, soft tissues, peritoneal cavity (linings?), prostate, preputial gland (occasionally), testes, uterus/vagina, ovaries were examined and had lesions in addition to the organs mentioned above. Based on the data as presented, none of these tissue types had neoplasms in the higher dose groups in a manner suggestive of a relationship to the presence of the test material in the diet. Occasionally, there were some tumor types which were present only in the higher dosed groups, but these types were not unusual and they were present as only 1 or 2 incidences.

Rare tumor types noted in this study included: dysgerminoma (mid dose group female, ovarian); reticulosis of the brain (malignant, in a male rat dosed with 5 ppm); and mesothelioma in the scrotum (a control male).

CONCLUSION: CORE classification of the chronic feeding aspects of this study is RESERVED.

1. The NOEL for this study is tentatively set at 1 part per million. At 5 ppm and above there is noted in males higher incidences of a lesion in the lung described as "medial muscle hypertrophy." The nature of this lesion must be further clarified and the registrant must provide a defense that the lesion is not induced by the test material (fenpropathrin).

   Aside from the apparent lesion of "medial muscle hypertrophy" in males, the NOEL is otherwise set at 125 ppm and the LEL is 500 ppm. At 500 ppm (HDT) there is some slight weight loss in females.

2. As an oncogenicity study in rats, this study is CORE MINIMUM. No oncogenic effect of the test material is noted at dose levels up to and including 125 ppm is recognized.

   The dose level of 125 ppm is considered the upper level for no oncogenic effects because the rats in this group were combined with the rats in the 500 ppm group. [See memos of correspondence between R. Engler and B. Litt and from B. Fisher to E. Budd attached concerning the statistical analyses of the rat tumor data.]

<u>The Metabolism of WL-41706 (S-3206) in mammals. The fate of a single oral dose of [^{14}C] WL-41706 in the rat.</u>

Shell Research Ltd., August 1980, #TLGR 0071.75
EPA Acc. No. 249938. Tab 111-c-6.

In the main phase of this experiment, ring-labeled ^{14}C fenpropathrin was dosed orally to 6 male and 6 female rats (Charles River, CD strain) at a dose level of 1.5 mg/kg of test chemical dissolved in corn oil. The urine and feces were collected for a period of 192 hours (8 days). 2 rats of each sex were sacrificed after 24 hours and 72 hours, the last 2 rats were sacrificed on the 8th day. The blood, kidney, liver, brain, guts, skin, fat, muscle and remaining carcass were analyzed for ^{14}C activity.

Excretion was rapid, approximately 97% was eliminated in 48 hours. Total recoveries were 104% for the male rats and 97% of the females rats. Of this, 54.5% (males) and 27.8% (females) was recovered in the feces. Less than 1.5% of the dose remained in the carcass. Analysis of the carcass tissue indicated that by day 8 residue levels were 0.01 ug/gm of tissue or less except for fat which was 0.2 ug/gm. At day 1 the tissue residues of fat were 0.5-0.6 and liver had levels of 0.4 to 0.6. A separate experiment was run using 2 additional rats to assess the extent to which the label expired as $^{14}CO_2$. Only 0.005% of the dose was expired by this route.

This study is CORE MINIMUM and demonstrates that fenpropathrin is rapidly excreted once ingested. There is little residue retained in the tissues with the highest levels (0.2 ug/gm at day 8) retained in the fat.

Metabolic fate of [^{14}C] WL-41706 (S-3206) in rats.

Shell Research Ltd., #TLGR 0034. 76, August 1980
EPA Accession No. 249938, Tab. 111-c-6.

Note: The urine from the rats used in the study reviewed above and dosed with ring-labelled fenpropathrin was saved and the results of attempting to characterize the metabolites are reported in this study. In addition, rats were dosed with ^{14}C cyclopropyl labelled fenpropathrin and the urine collected and attempts to characterize the urinary metabolites were made. A third aspect of this study included making a bile duct cannalula and collecting bile from rats dosed intraperitoneally with labelled fenpropathrin.

The metabolites were characterized by combinations of hydrolysis (chemical and/or enzymatic), gas chromatography and high pressure liquid chromatography as well as TLC. Comparison with standards and mass spectrometry were also used to assist in the characterization of the metabolites.

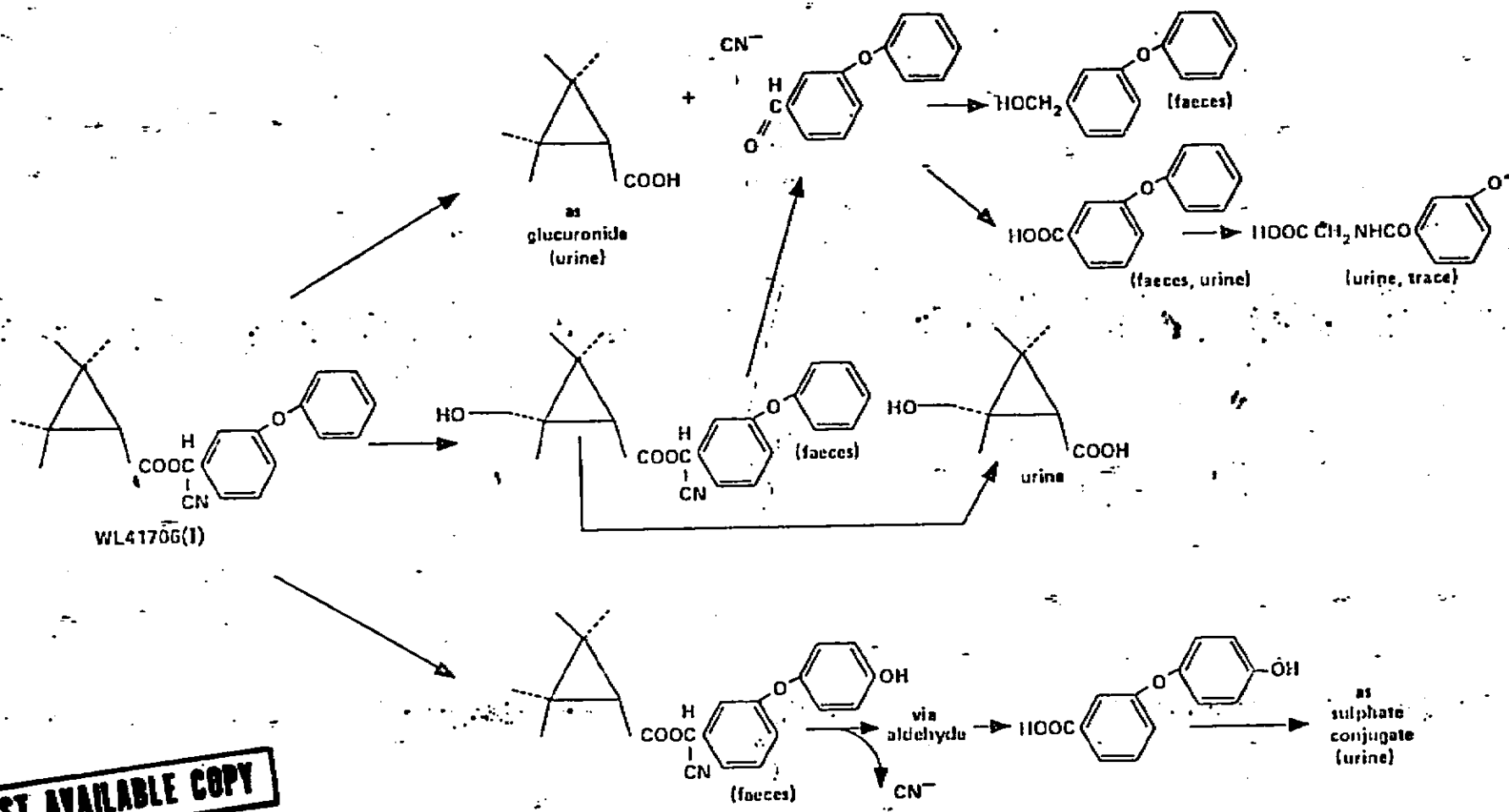


Fig 3 The major transformations of WL 41706 in rats.

Zeroxed From the Study report. JA

The principal metabolites identified for fenpropathrin in the urine, feces and bile are shown in the attached figure (Figure 3) which was xeroxed from the study report.

Quantitatively, 90% of the urinary metabolite derived from ^{14}C benzyl fenpropathrin was an O-sulfate conjugate of 3-(p-hydroxyphenoxy) benzoic acid. The most important metabolites of ^{14}C cyclopropyl fenpropathrin were 2-trans-hydroxymethyl-2-methyl-3,3-dimethylcyclopropane carboxylic acid, and 2,2,3,3-tetramethylcyclopropanecarboxylic acid glucuronide.

These data indicate that fenpropathrin is hydrolyzed at the ester site to yield products which are hydroxylated and conjugated to give several metabolites in urine and feces (see Figure 3).

This study is CORE MINIMUM. The metabolic pathway in rats for fenpropathrin has been delineated to indicate the major route of metabolism and identification of the major metabolites.

004567

Autoradiographic assessment of DNA repair in mammalian cells after exposure to S-3206 (Fenpropathrin).

Huntington Research Centre, SMO 143/81881, June 16, 1982
EPA Accession No. 249938, Tab. IV-D-6.

In this study, human Hela S3 epithelioid cells derived from a human cervical carcinoma were assaulted with the test material (S-3206, batch number 0-113, purity was not stated) and with positive controls 4-nitro-quinoline 1-oxide (4NQO) used in the absence of the S-9 mix and 2-aminoanthroacene (2-AA) used in the presence of the S-9 mix. The purpose of this study is to investigate whether or not test materials cause DNA damage that is later repaired. The extent of repair is estimated by the incorporation ^{3}H-thymidine into the repairing DNA which can be determined autoradiographically. In this study, two successive DNA repair tests were run and S-3206 was tested over the range of 200, 400, 800, 1600 and 3200 ug/ml, dose levels at which the test material precipitated out of the solution. A preliminary study established that dose levels up to and including 2500 ug/ml (HDT) were not toxic to the cells. It should be noted that it is desirable to test for DNA damage repair at dose levels which cause some degree of toxicity.

S-3206 did not present evidence of causing DNA damage in this study. The positive control (4NQ8) for the study in the absence of S-9 mix responded as expected. The positive control (2-AA) for the portion of the study with the S-9 mix produced only a minimum positive response.

This study has deficiencies in that the S-3206 was insoluble in the assay medium and the positive control for the S-9 mix did not respond clearly. The results of this study are INCONCLUSIVE.

Studies on the DNA-damaging capacity of S-3206 with Bacillus subtilis.

Research Dept. Sumitomo Chemicals, August 1980, FT-00-0038 EPA Accession No. 249938, Tab. IV-D-2.

Dose levels of 0, 10, 50, 100, 500, 1000, 5000 ug/paper disk of S-3206 were tested in the rec-assay for DNA-damaging capacity using the strains Bacillus subtilis M 45 rec- and H17. The test consisted of applying the cultured suspension of bacteria (0.1 ml of H17 or 0.2 ml of M45) to the top of an agar plate, then a paper disk containing the test substance (S-3206 97% pure from lot #022018) was placed into the center of the plate. The diameter of growth inhibition zone was measured after 24 hours incubation at 37 °C. The positive control was N-methyl-N-nitro-N-nitrosoguanidine (MNNG), and the negative control was kanamycin.

No inhibition zone (greater than the DMSO control) was noted for any level of S-3206 tested. The positive control (MNNG) produced inhibition in both the M45 rec- and H17 (wild) strains; the negative control produced inhibition in the M45 (rec-) assay only. The summary table showed the results of 2 replicates of 4 plates.

This study is considered by TB geneticist to be ACCEPTABLE and the test material was not shown to be mutagenic under the conditions of the assay.

Toxicity studies with WL-41706 (S-3206): Chromosome studies on bone marrow cells of Chinese hamsters after two daily oral doses of WL-41706.

Shell Tunstall Research Lab, #TLGR.0104.75, December 1975. EPA Accession No. 249938, Tab. IV-D-3.

Four groups of 12 Chinese hamsters (6 males and 6 females) were dosed as either controls, 10 mg/kg or 20 mg/kg of WL-41706 (batch #24, 97.0% purity supplied by the Woodstock Laboratory) and a fourth group received 100 mg/kg of cyclophosphamide (the positive control). All dosing was intraperitoneally. Dosing with these agents was done on two successive days. At 8 and 24 hours after the second dose the hamsters were sacrificed using CO_2 gas and their femurs removed. Ninety minutes prior to sacrifice the hamsters were dosed with 0.4% Colcemid to arrest mitosis. It was stated that where possible 100 cells were analyzed from the bone marrow of each animal. Note: the dose levels selected are 1/8 and 1/4 of the LD_{50} for WL-41706.

The hamsters dosed with WL-41706 did not present evidence of increases in polyploidy, chromatid gaps, chromatid breaks, acentric fragments, exchange figures, or multiple chromosome breakage. The positive control produced the expected positive response.

Current criteria for an acceptable study of this type requires that the dosed animals show clear signs of systemic toxicity. There is no way of knowing if the test material was absorbed and reached the bone marrow. The results of this study are thus INCONCLUSIVE.

Studies on mutagenicity of some pyrethroids on Salmonella strains in the presence of mouse hepatic S9 fractions.

Sumitomo Chemical Co. Institute for Biological Science, August 4, 1977, AT-70-0157.
EPA Accession No. 249938, Tab. IV-D-4.

S-9 preparations were obtained from the livers of 6 strains of mice treated with PCB (the conditions of treatment and preparation of the S-9 fraction were not presented) and the mutagenic (if any) effects of four novel pyrethroids were tested. These pyrethroids were S-3206 (lot #G22018, 97% purity) and S-5602, NRDC-143 and NRDC-149. S-3206 was tested in strains TA98, TA100, TA1535, TA1537 and TA1538 of Salmonella typhimurium at dose levels of 0, 10, 100, 1000ug/plate.

S-3206 did not show evidence of producing a mutagenic effect. The other pyrethroids tested (at the same dose levels) also did not present evidence of a positive effect. The positive controls produced the expected positive results. This study is unacceptable.

This study is UNACCEPTABLE as per discussion with Dr. I. Mauer, Geneticist, Toxixology Branch. Current criteria for acceptable studies of this type require that evidence of cytotoxicity of the test materials be demonstrated and that the test dose levels include those levels at which cell toxicity results. Thus, the unacceptability of this study is related to insufficient dose levels being tested.

Toxicity studies with WL-41706 (S-3206); Mutagenicity studies with WL-41706 in the host mediated assay.

Shell Research Ltd., TLGR.0003.76, August 1980.
EPA Accession No. 249938, Tab. IV-D-5.

Four groups of mice were dosed with either solvent control, 10 mg/kg or 20 mg/kg of WL-41706 (batch 24. 97.0% purity); each of these groups had 3 mice per group; the fourth group was dosed with 400 mg/kg of ethyl methanesulfonate. Shortly after this dosing, the mice were injected with pooled yeast cell culture (Saccharomyces cerevisiae strain JD1). Five hours after dosing, the mice were sacrificed and the yeast cells harvested from the dead mice. Three replicates of this experiment were run. The harvested yeast cells were then seeded on four synthetic agar plates without tryptophan and four without histidine. The plates were then incubated at 38 °C for four days.

No effects of dosing with WL-41706 on the number of convertants/10^6 survivors for either the histidine locus or the tryptophan locus were reported. The positive control consistently produced the expected positive result for both the histidine and tryptophan locus. [redacted]

This study is UNACCEPTABLE. This type of study has inherent problems when chemicals such as the pyrethroids used are rapidly metabolized and conjugated. For example, there is no evidence that the test material or its metabolites actually reached the target cells.

An assessment of the mutagenic potential of S-3206 using an in vitro mammalian cell test system.

Huntington Research Centre, England, #SMO 144/8252 March 25, 1982 EPA Accession No. 249938, Tab. IV-D-1.

For this study the test material used was S-3206 from batch 01113. The positive controls were methane sulphonate (tested at 500 ug/ml) md 20-methylcholanthrene (tested at 15 ug/ml); the former agent was used in the absence of the S-9 metabolic activation system and the latter compound was used in the presence of the S-9 mixture. The test materials were dissolved in DMSO.

The cell line used in this study was the mouse lymphoma L51784 and were heterozygous for the thymidine kinase locus ($TK^{+}/^{-}$). The principle of this assay involves the mutagenic conversion of the cells to the homozygous thymidine kinase deficient form ($TK^{-}/^{-}$). The homozygous form is capable of growing in the presence of trifluorothymidine.

The study to define the mutagenic potential of S-3206 was preceded by a preliminary toxicity test in which S-3206 was assesed for cellular toxicity at 31.25, 62.5, 125, 250, 500, and 1000 ug/ml. The report summary states that S-3206 was moderately toxic to the cells and in the presence of the S-9 mix, the toxicity of S-3206 was marginally increased. No data were presented to substantiate the results of the preliminary test.

The mutation test conducted in the absence of the S-9 mixture was assessed at 50.3, 84.5, 141.9, 238.2, and 400 ug/ml of S-3206. In this study about 44% suspension growth was noted at the test level of 141.9 meaning that the test levels of S-3206 were toxic to the cells (even the dose level of 50.3 ug/plate resulted in 64% of the control value for suspension growth). The viability and mutation of the L51784 cells were assessed for cells of colony diameter of $\geq$0.2 and $\geq$0.4 millimeter. The following table shows the results:

	Mean Mutation Frequency	
	Colony $\geq$ 0.2 mm	Colony $\geq$ 0.4 mm
Control	78.8	48
50.3 ug/ml	82.8	41
84.5 ug/ml	114.4	71
141.9 ug/ml	110.9	63
238.2 ug/ml	128.9	79.5
EMS ug/ml	856.7***	548***

*** P < 0.001

There is noted a slight increase for the higher dose for both cell sizes and for the cells of ≥0.2 mm the mean mutation frequency progressively increases as the test level increases. However, the magnitude of the increases in the mean mutation frequency is less than 2x the control value for S-3206 and is much lower than the value for the positive control (EMS).

The mutation test conducted in the presence of the S-9 mixture was tested at dose levels of 0, 30, 47.5, 75.3, 119.4, 189.2 and 300 ug/ml. At the test level of 189.2 it was noted that the suspension growth was 33% of the control value. The following table shows the mean mutation frequency obtained in the presence of the S-9 mixture.

	Mean Mutation Frequency	
	Colony ≥ 0.2 mm	Colony ≥ 0.4 mm
Control	79	50.5
47.5 ug/ml	129	81.5
75.3 ug/ml	92.5	45.5
119.4 ug/ml	144*	88.0
189.2 ug/ml	138.5*	76.5
20-MC	495.5***	270.0***

* $P < 0.05$
*** $P < 0.001$

This study shows a statistically significant increase at the test levels of 119.4 and 189.2 ug/ml. As per discussion with Dr. W. Schneider of Tox Branch, this is an equivocal result that is at best weak and is of no significance or concern if other tests (mutagenesis) are negative.

Note: The test laboratory and the registrants also agree that the study does show a possibly positive result but consider the result to be equivocal. This study is acceptable.

Acute Oral Toxicity of S-3206 10% EC in Mice

Sumitomo Chemical Company Institute for Biological Sciences
FT-80-0020, January 1979. EPA Accession No. 249937
Tab IV-A-10.

Five groups of 10 male and 10 female mice were dosed with test material (S-3206, 10% emulsifiable concentrate lot #48937) suspended in water at dose levels of 100, 130 170, 220 and 285 mg/kg and observed for 2 weeks. These mice were not fasted (apparently) prior to test chemical administration.

LD_{50}s of
162 (144-182) mg/kg for males
164 (148-182) mg/kg for females.

were determined.

No table illustrating the time of onset and duration or the time of death was presented. It was stated that deaths were observed within 1 to 2 hours post-treatment and that the toxic signs in surviving mice disappeared within 24 hours. The toxic symptoms reported included decreased spontaneous motor activity, muscular fibrillation, tremor, salivation, incontinence of urine, hypersensitivity, lacrimation, dyspnea, lesser appetite, hind limb ataxia, and loss of the righting reflex.

This study is CORE SUPPLEMENTARY. The data are in narrative form. Mice are not the preferred species for determining the LD_{50} for label purposes.

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